Sponsor

Novartis

Generic Drug Name

LCZ696

Therapeutic Area of Trial

Heart Failure

Approved Indication

none

Study Number

CLCZ696A2117

Title

An open label, non-randomized study to explore safety/tolerability, pharmacokinetics and pharmacodynamics of LCZ696 in patients with stable heart failure

Phase of Development

Phase II

Study Start/End Dates

4 May 2009 (first subject dosed)
9 July 2009 (last subject dosed)

Study Design/Methodology

This study was an open label, non-randomized study to explore safety/tolerability, pharmacokinetics and pharmacodynamics of LCZ696 in stable patients with HF (NYHA class II-IV).

Centres

Two sites in Moscow, Russia

Publication

None

Objectives

Primary objectives

To assess the safety (including blood pressure, renal function and serum electrolytes) and tolerability of LCZ696 200 mg BID treatment in stable heart failure (HF) patients

To determine the pharmacokinetics of LCZ696 following BID dosing in HF patients

Secondary objectives

To examine the effect of LCZ696 on:

Urinary volume, sodium excretion

Plasma and urine ANP, cGMP, BNP and NT-proBNP

Renin/angiotensin/aldosterone pathway and other biomarkers

Test Product, Doses, and Mode of Administration

Each patient participated in a screening period of up to four weeks, then entered a 7-day dose titration period with 100 mg LCZ696 BID, followed by a 14-day treatment with 200 mg LCZ696 BID. LCZ696 will be given as tablets orally.

Reference Product(s), Dose(s), and Mode(s) of Administration

N/A

Criteria for Evaluation

Safety and tolerability assessments

Safety and tolerability assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs) with their severity and relationship to study drug, concomitant medications/significant non-drug therapies and medications taken prior to first dosing. They also included regular monitoring of vital signs and body measurements (height, weight, temperature, blood pressure, and pulse rate), electrocardiogram (ECG) evaluation, hematology, blood chemistry and urinalysis.

Pharmacokinetic assessments

Plasma samples were collected on Day 7; Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hrs post morning dose and Day 21; Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72 hours post morning dose.

Valsartan, AHU377 and LBQ657 in plasma have been analyzed using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method, with a lower limit of quantification (LLOQ) at 1.0 ng/mL for all three analytes.

Pharmacodynamic assessments

Analysis of plasma for pharmacodynamic effects:

ANP, cGMP. BNP, NT-proBNP, aldosterone, plasma renin concentration and activity (PRC and PRA), endothelin, mid-region pro-adrenomodulin, insulin, glucose were measured on Day 1, 7 and 21; Pre-dose, 4, 12, 16 and 24 hours post morning dose.

Analysis of urine for pharmacodynamic effects:

On Day 1, 7, 21, 24-hour urine was collected as 2 twelve-hour samples to measure volume, sodium, potassium, calcium, uric acid, creatinine, ANP, cGMP, BNP, NT-proBNP and aldosterone

Ambulatory BP measurement (ABPM)

On Day 1, 7, 21, 24-hour ABPM were performed with a portable recording system placed on the non-dominant arm. Measurements included mean 24-hour systolic and diastolic pressures, as well as daytime values (measured every 15 minutes from 8 a.m. to 10 p.m.) and night-time values (measured every 20 minutes from 10 p.m. to 8 a.m.).

Statistical Methods

Safety data analysis
Safety data will be listed and summarized by treatment and day/hour within the treatment, if applicable.
PK data analysis
Descriptive statistics (including mean, SD, CV, Geo-mean, median, min and max) was provided for all pharmacokinetic parameters after 7 days on 100mg BID (Day 7) and after 14 days on 200mg BID treatment (Day 21).

PD data analysis

Descriptive statistics (including mean, SD, CV, Geo-mean, median, min and max) was provided for the 24 mean ambulatory BP measurement and other PD biomarkers from plasma or urine on baseline, after 7 days on 100mg BID and after 14 days on 200mg BID treatment, and change from baseline to 7 days on 100mg BID and 14 days on 200mg BID treatment. The AUE0-24hr of plasma PD biomarkers was calculated after 7 days on 100mg BID and after 14 days on 200mg BID treatment, and the descriptive statistics was provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Male and/or female subjects of at least 18 years of age; females must not be of childbearing potential; Left ventricular ejection fraction ≤ 40%; Patients with a sitting systolic blood pressure ≥110 mm Hg at randomization (Visit 2); Patients with an eGFR ≥ 30 ml/min/1.73 m2 at Screening (calculated by the Modification of Diet in Renal Disease formula); Patients with a potassium ≤ 5.2 mmol/l at Screening

Exclusion Criteria

Isolated right heart failure due to pulmonary disease; Diagnosis of postpartum cardiomyopathy; Hemodynamically significant vavular disease (e.g. mitral stenosis or lesions of the left ventricular outflow tract including aortic stenosis or hypertrophic obstructive cardiomyopathy); Secondary forms of cardiomyopathy such as restrictive cardiomyopathy or infective cardiomyopathy; Patients with a history of heart transplant or who were on a transplant list (life expectancy < 6 months at time of entry into the study); Patients with sitting systolic blood pressure < 110 mm Hg or > 160 mm Hg at Visit 2; Patients on both ACEi and ARB, ACEi and DRI, ARB and DRI treatment, or on all three medications at Screening; Coronary artery disease likely to require coronary artery bypass graft (CABG) or PTCA during the 4 weeks of the trial. Patients with stable angina pectoris requiring pharmacological therapy are allowed entry into the study; History of myocardial infarction, unstable angina, coronary bypass surgery or any percutaneous coronary intervention (PCI), stroke or TIA during the 6 months prior to Screening; Clinically significant second or third degree heart block without a pacemaker; Patients with an implantable cardioverter defibrillator (ICD) that has discharged in the past 3 months; Patients with a biventricular pacemaker (CRT) implanted within 6 months of Screening; Episode(s) of ventricular tachycardia or another severe arrhythmia producing significant hemodynamic consequences or considered life-threatening within the last 3 months; Breathlessness and/or edema from non-cardiac causes, such as lung disease, anemia, or severe obesity (BMI >40 kg/m2); Patients with a known history of angioedema; Significant laboratory abnormalities; A history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.

All subjects provided written informed consent prior study entry

Number of Subjects

	Novartis product	Comparator
Planned N	30 (100 %)	N/A
Randomised n	30 (100 %)	N/A
Intent-to-treat population (ITT) n (%)	30 (100 %)	N/A
Completed n (%)	27 (90 %)	N/A
Withdrawn n (%)	3 (10%)	N/A
Withdrawn due to adverse events n (%)	3 (10%)	N/A
Withdrawn due to lack of efficacy n (%)	0	N/A
Withdrawn for other reasons n (%)	0	N/A

Demographic and Background Characteristics

N (Safety)	30 (100 %)	
N (PD, PK)	30 (100 %)	
Females : males	5 (16.7 %) : 25	
Mean age, years (SD)	62.0 (9.30)	
Mean weight, kg (SD)	92.50 (16.05)	
Race Caucasian n (%)	30 (100 %)	

Primary Objective Results

Safety Results, see Safety section below.

Pharmacokinetic Results

Summary of the mean (SD) PK parameters for AHU377, LBQ657 and valsartan on Day 7 following administration of 100 mg LCZ696 BID in HF patients (N=30)

Analyte	Tmax (hr)	Cmax (ng/mL)	AUC0-12 (hr*ng/mL)
AHU377	0.7 (0.4)	1229 (621.3)	1537 (730.7)
LBQ657	2.8 (1.5)	9103 (3174)	82633 (33740)
Valsartan	2.2 (0.8)	3814 (1504)	25888 (12096)

Summary of the mean (SD) PK parameters for AHU377, LBQ657 and valsartan after 14 days of 200 mg LCZ696 BID administration in HF patients (N=27)

Analyte	Tmax (hr)	Cmax (ng/mL)	AUC0-12 (hr*ng/mL)	CLss_F (L/hr)	Vz_F (L)	T1/2 (hr)
AHU377	0.8 (0.3)	2408 (1357)	3153 (1377)	36.2 (14.6)	194.1 (138.3)	3.9 (3.6)
LBQ657	2.6 (1.1)	16345 (4704)	147111 (51762)	ND	ND	18.4 (6.8)
Valsartan	2.1 (0.4)	6044 (2502)	38807 (18129)	3.1 (1.1)	58.2 (24.7)	13.7 (5)

Secondary Objective Results

The PD analysis is not yet completed.

Safety Results

Adverse Events by System Organ Class

Adverse events overall and frequently affected system organ classes - n (%) of subjects (all subjects)

	LCZ696 100mg BID N=30 n(%)	LCZ696 200mg BID N=30 n(%)	Total N=30 n(%)
Subjects with AE(s)	16 (53.3)	15 (50.0)	21 (70.0)
System organ class			
Cardiac disorders	6 (20.0)	5 (16.7)	8 (26.7)
Nervous system disorders	4 (13.3)	3 (10.0)	7 (23.3)
Psychiatric disorders	2 (6.7)	1 (3.3)	3 (10.0)
Blood and lymphatic system disorders	1 (3.3)	0 (0.0)	1 (3.3)
Metabolism and nutrition disorders	0 (0.0)	1 (3.3)	1 (3.3)
Renal and urinary disorders	1 (3.3)	0 (0.0)	1 (3.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (3.3)	1 (3.3)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (3.3)	1 (3.3)

SOC arranged by total frequency of both treatment groups

Adverse events overall and most frequent events - n (%) of subjects (all subjects)

	LCZ696 100mg BID N=30 n(%)	LCZ696 200mg BID N=30 n(%)	Total N=30 n(%)
Subjects with AE(s)	16 (53.3)	15 (50.0)	21 (70.0)
Preferred term			
Atrioventricular block first degree	1 (3.3)	3 (10.0)	4 (13.3)
Blood creatinine increased	2 (6.7)	2 (6.7)	4 (13.3)
Blood potassium increased	1 (3.3)	3 (10.0)	4 (13.3)
Dizziness	2 (6.7)	2 (6.7)	4 (13.3)

Electrocardiogram QT prolonged	2 (6.7)	2 (6.7)	3 (10.0)
Ventricular extrasystoles	1 (3.3)	3 (10.0)	3 (10.0)
Blood triglycerides increased	3 (10.0)	0 (0.0)	3 (10.0)
Headache	1 (3.3)	2 (6.7)	3 (10.0)
Sinus bradycardia	2 (6.7)	1 (3.3)	2 (6.7)
Insomnia	1 (3.3)	1 (3.3)	2 (6.7)
Lipase increased	1 (3.3)	1 (3.3)	2 (6.7)
Tachycardia	2 (6.7)	0 (0.0)	2 (6.7)
Blood bilirubin increased	1 (3.3)	0 (0.0)	1 (3.3)
Blood calcium increased	1 (3.3)	0 (0.0)	1 (3.3)
Blood urea increased	1 (3.3)	0 (0.0)	1 (3.3)
Blood uric acid increased	1 (3.3)	0 (0.0)	1 (3.3)
Bundle branch block left	0 (0.0)	1 (3.3)	1 (3.3)
Cardiac failure	0 (0.0)	1 (3.3)	1 (3.3)
Cough	0 (0.0)	1 (3.3)	1 (3.3)
Hematuria	1 (3.3)	0 (0.0)	1 (3.3)
Hypoglycemic unconsciousness	0 (0.0)	1 (3.3)	1 (3.3)
Leukocyturia	1 (3.3)	0 (0.0)	1 (3.3)
Loss of consciousness	1 (3.3)	0 (0.0)	1 (3.3)
Nightmare	1 (3.3)	0 (0.0)	1 (3.3)
Platelet count decreased	0 (0.0)	1 (3.3)	1 (3.3)
Pruritus	0 (0.0)	1 (3.3)	1 (3.3)
Somnolence	0 (0.0)	1 (3.3)	1 (3.3)
Supraventricular extrasystoles	1 (3.3)	0 (0.0)	1 (3.3)
Thrombocytopenia	1 (3.3)	0 (0.0)	1 (3.3)

Preferred term arranged by total frequency of both treatment groups

The pharmacodynamic analysis is not yet completed.
Serious Adverse Events and Deaths No serious adverse events, or deaths were reported during the study.
Other Relevant Findings None
Date of Clinical Trial Report Completion pending
Date Inclusion on Novartis Clinical Trial Results Database 9 Jul 2010 Date posted to the CTRD
Date of Latest Update 9 Jul 2010